Cardiovascular adverse effects of metoclopramide: Review of literature

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ABSTRACT

Introduction: Articles pertaining to reports and clinical or pharmacological research for cardiovascular adverse effects of metoclopramide were identified via a search of MEDLINE (1966-February 2012), SCOPUS, and Google Scholar. Objective: To review the reports in literature of patients receiving metoclopramide who suffered from cardiac arrest, bradycardia, total heart block, acute hypotension, supraventricular tachycardia, circulatory collapse, QT prolongation, Torsade de Pointes, ST depression, and congestive heart failure. Discussion: In most cases the reactions occurred immediately after administration of metoclopramide, were associated with normal doses administered via intravenous or central lines, and resolved. Rechallenge occurred in several cases. The likelihood of these events occurring and the mechanism by which metoclopramide affects the cardiovascular system is unclear, however, it has been shown to have a direct effect on the heart, block presynaptic autoreceptors and enhance catecholamine release, enhance cholinergic neurotransmission and cause 5-HT3 receptor blockade and 5-HT4 receptor antagonism. Conclusion: Due to cardiovascular risks associated with the use of IV metoclopramide, recommendations are to monitor patients and report these events.

Keywords: Metoclopramide, Cardiovascular, Adverse drug reactions, Case reports, Cardiac

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INTRODUCTION

Metoclopramide (1,4-amino-5-chloro-2 methoxy-N-(2-diethyl-aminoethyl) benzamide), a dopaminergic antagonist structurally related to procainamide, is an effective agent in treating and preventing vomiting and is useful in esophageal reflux disease, gastroparesis, dyspepsia and other gastrointestinal disorders. It promotes gastric emptying prior to anesthesia and reduces post-operative vomiting, possibly by blocking the chemoreceptor trigger zone for vomiting [1].

Although metoclopramide has been available for decades, its side effect profile continues to evolve. In 2009, the Food and Drug Administration (FDA) required a Black Box warning regarding the increased risk of tardive dyskinesia when metoclopramide is used at high doses or over long periods of time. Today, over 1,000 lawsuits claiming tardive dyskinesia from metoclopramide are pending in New Jersey courts alone [2]. Reports of cardiovascular adverse effects from metoclopramide first appeared in the literature in 1974,
when Shaklai et al. noted cardiac arrhythmias, specifically multifocal preventricular contractions (PVCs) which resolved within one hour and reoccurred upon rechallenge [3]. Since then, a number of case reports have appeared in literature.

**OBJECTIVE**

The aim of this study is to review all available reports and patient series of metoclopramide induced cardiovascular (CV) adverse effects and provide recommendations for clinicians.

**DISCUSSION**

Metoclopramide is a benzamide derivative having various physiologic effects with side effects occurring in 10–20% of patients [4]. The most common side effects include drowsiness, GI disturbances, extrapyramidal reactions and increased lactation [5]. Metoclopramide has long been considered to lack significant CV effects. However, conflicting literature for CV effects of metoclopramide has appeared and will be discussed. In large doses in patients with heart disease, metoclopramide had no marked influence on hemodynamic parameters [6]. In animal studies, metoclopramide had a negligible effect on blood pressure (BP) responses to acetylcholine, adrenaline, histamine and noradrenaline [7]. The drug has been found to block the hypotensive action of dopamine. Cardiac conduction is unaffected by metoclopramide, but in animal studies large doses prevented experimentally-induced cardiac arrhythmias and produced a slight blood pressure decrease [1]. Careful consideration should be given to examine the risks and benefits of using metoclopramide for preoperative prophylaxis of nausea and vomiting.

**Study Method:** To identify pertinent literature, including but not limited to case reports describing CV adverse reactions from use of metoclopramide, we conducted a search using MEDLINE (1966- to February 2012), SCOPUS and Google Scholar engine using the search terms: adverse effects, metoclopramide, cardiac, cardiovascular, cardiac arrest, sinus arrest, bradycardia, tachycardia, arrhythmia, QT prolongation, Torsade de Pointes, hypotension and a combination of text and MeSH terms. Bibliographies of identified articles were subsequently reviewed for additional citations.

**Review of Cases in the Literature:** Cases of sinus or cardiac arrest [8–15], bradycardia followed by total heart block [14, 16–18], acute hypotension [19–24], and circulatory collapse [24] have been reported with metoclopramide. The duration of the cardiac arrest reported in the cases is mostly between 15–30 sec, but on one occasion it lasted two min [11]. Several cases describe extreme bradycardia [9, 10, 12, 14, 16]. Others have reported cardiac arrhythmias such as QT prolongation [25–27], Torsade de Pointes [13, 26, 28, 29], supraventricular tachycardia (SVT) [28, 30–32] and ST depression [28, 30]. Cases of congestive heart failure have occurred following chronic metoclopramide at doses of 40 mg/day [31]. In patients with heart failure, metoclopramide at doses of 10 mg three times a day blunted the natriuretic response to saline load [34]. The authors concluded that metoclopramide should be used with caution in heart failure patients and those with volume overload. Single IV doses of 10 mg decreased diastolic BP in women with pregnancy-induced hypertension and increased plasma aldosterone in every subject [35]. However, the increase in plasma aldosterone was greater in women with pregnancy-induced hypertension than in normal pregnant women (p < 0.05). Congestive heart failure is most likely due to a different mechanism of action as dopaminergic inhibition is thought to result in increases in plasma aldosterone, thereby producing sodium retention [30]. The summary of key cases retrieved is presented in table 1.

A number of cardiovascular adverse effects are listed in the metoclopramide prescribing information, including AV block, bradycardia, heart failure, hypertension/hypotension, SVT but not circulatory collapse, cardiac arrest, Torsade de Pointes, QT prolongation, and ST depression [36].

Rechallenge with metoclopramide occurred in a number of cases. Lau et al. reported two separate episodes of circulatory collapse following IV metoclopramide [24]. Bentsen et al. reported five repeated episodes of cardiac arrest following five separate metoclopramide injections over 48 hours [11]. Unusual drug reactions may arise as a result of multiple factors. Suggested underlying predisposing or contributory factors for development of cardiac adverse effects with metoclopramide include previous cardiovascular disease, atrial fibrillation [8], autonomous dysfunction [15], hyperbilirubinemia [11], halothane anesthesia [19, 21], and pericardial drainage tube [16]. However, in other cases there has been no clear association with any risk factors. For example, cardiac arrest following metoclopramide has been reported in patients without known cardiac disease [13].

**Risk Factors:** Neither age nor dose appears to be contributory factors for cardiovascular adverse reactions from metoclopramide. While the patients in most of the cases were elderly, cardiac arrest, for example, following metoclopramide has occurred in middle-aged individuals as well [11]. However, no case reports in pediatric patients were found. Rose et al. observed that rapidly administered IV metoclopramide at 0.25 mg/kg had no effect on either heart rate or BP in 45 children between the ages of 2–16 years old prior to elective surgery [37]. However, in adult patients, Blanco et al. observed that IV metoclopramide decreased BP in both normotensive and hypertensive adults with greater decreases in the later [38]. Other studies have also demonstrated vascular hyperreactivity during cold pressor test (CPT) with metoclopramide at doses of 7.5 mcg/kg/min during a 30 minute period in both normotensive and hypertensive patients [39]. Metoclopramide significantly decreased BP but did not
Table 1. Published case reports of M-associated cardiac adverse drug events.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient Information</th>
<th>M dose and concomitant medications</th>
<th>Description of Event</th>
<th>Probability of Causation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shaklai et al. (1974) [3]</td>
<td>55-year-old female complaining of vomiting</td>
<td>Given M 10 mg IM; no other medications given</td>
<td>Within 15 min, developed palpitations, irregular pulse; ECG revealed multifocal preventricular contractions. Lasted one hour</td>
<td>M rechallenged and patient experienced same rhythm disturbances</td>
</tr>
<tr>
<td>Park et al. (1978) [22]</td>
<td>Case series of patients undergoing intracranial aneurysm repair (N=4)</td>
<td>Under general anesthesia immediately prior to M IV (central venous line) administration</td>
<td>All four patients experienced an immediate decrease in blood pressure and increase in heart rate</td>
<td>Temporal relationship established Anesthesia may have potentiated hypotensive effect</td>
</tr>
<tr>
<td>Pegg et al. (1980) [21]</td>
<td>Case series of patients undergoing neurosurgery (N=16)</td>
<td>Given M 10 mg IV perioperatively; all patients had been under general anesthesia immediately prior. Majority of patients did not receive any ganglion blocking agent</td>
<td>Average decrease in systolic pressure of 20%, and average decrease in diastolic pressure of 22% maximum decline in BP occurred 44 sec after administration, resolving within 96 sec</td>
<td>Temporal relationship established Anesthesia may have potentiated hypotensive effect</td>
</tr>
<tr>
<td>Park et al. (1981) [19]</td>
<td>Case series of healthy, non-anesthetized male patients. (N=6)</td>
<td>Given M IV. Patients were in the supine position during administration</td>
<td>Within 30 sec, all patients had a decrease in BP and increase in heart rate; all patients normalized within 60-90 sec</td>
<td>Temporal relationship established</td>
</tr>
<tr>
<td>Hughes et al. (1984) [20]</td>
<td>40-year-old female</td>
<td>Anesthetized for a hysterectomy; given M 10 mg IV perioperatively</td>
<td>Within 30 s, developed bigeminy (44/min); reverted to normal sinus rhythm; normotensive upon administration of atropine 0.6 mg IV</td>
<td>Temporal relationship established Anesthesia may have potentiated hypotensive effect</td>
</tr>
<tr>
<td>Pollera et al. (1984) [8]</td>
<td>49-year-old woman given high-dose M (1 mg/kg) for four doses</td>
<td>Stage III ovarian cancer, receiving third course of intraperitoneal cisplatin; hexamethylmelamine (200 mg/day) was added on later</td>
<td>Patient had several dystonic episodes and was treated with diazepam and orphenadrine, six hours after the first dose of M, the patient went into cardiac arrest and died</td>
<td>Concomitant administration of M with hexamethylmelamine may have contributed to CNS toxicity</td>
</tr>
<tr>
<td>Name</td>
<td>Age/Gender/Comorbidity</td>
<td>Condition</td>
<td>Treatment</td>
<td>Outcome/Note</td>
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<tr>
<td>Withington et al. (1986) [9]</td>
<td>54-year-old male. Post pancreatectomy</td>
<td>Given M 10 mg IV as an anti-emetic. Patient underwent total pancreatectomy; post surgical complications include DVT, PE, chest infection; given dopamine for pressor support</td>
<td>Within 30 sec of M administration, developed sinus bradycardia, asystole for 25 sec, progressing to complete heart block and cardiac arrest; heart rate and BP spontaneously returned to normal.</td>
<td>Rechallenged with a smaller dose (5 mg) of M developed sinus bradycardia with a slight decrease in BP, both resolving within 45 sec.</td>
</tr>
<tr>
<td>Bevacqua et al. (1988) [28]</td>
<td>37-year-old postpartum female with no history of cardiac issues</td>
<td>Patient given M 10 mg IV preoperatively</td>
<td>Within one min, patient developed SVT (170 beats/min), resolving to sinus tachycardia with nonspecific ST segment changes on ECG after treatment</td>
<td>Temporal relationship established</td>
</tr>
<tr>
<td>Ahmad et al. (1991) [31]</td>
<td>54-year-old female, post-myocardial infarction, insulin-dependent diabetic</td>
<td>Patient given M 40 mg/day in divided doses (route unknown) for diabetic gastroparesis</td>
<td>After 72 hours of receiving M, developed acute congestive heart failure; symptoms resolved when M was discontinued</td>
<td>M inadvertently rechallenged, causing decompensated heart failure after 48 hours of M treatment</td>
</tr>
<tr>
<td>Midtunn et al. (1994) [16]</td>
<td>62-year-old male with lung emboli and atrial fibrillation</td>
<td>Patient given M 2.5 mg IV; concomitant digoxin</td>
<td>Within seconds, developed extreme bradycardia, followed by total heart block</td>
<td>Rechallenged with M 5 mg IV, again developing bradycardia and total heart block Concomitant digoxin may have contributed to heart block Temporal relationship established</td>
</tr>
<tr>
<td></td>
<td>71-year-old male with chronic lymphocytic leukemia patient and tubulointerstitial nephropathy</td>
<td>Patient given M 10mg IV. Patient also required dobutamine, norepinephrine, and dopamine for pressor support</td>
<td>Within seconds, patient developed bradycardia (heart rate decreased from 100 beat/min to 50 beats/min); spontaneously rebounded</td>
<td></td>
</tr>
<tr>
<td>Malkoff et al. (1995) [15]</td>
<td>51-year-old woman with respiratory failure, autonomic failure, and labile BP</td>
<td>Patient was given M 5 mg IV push every 6 hours, later increased to 20 mg. Other medications include ranitidine, antacids, and acetaminophen Vasoactive drugs include dopamine, phenylephrine, alternating with nitroprusside</td>
<td>Patient experienced repeated bradyarythmias 10-15 min following scheduled doses, of varying duration of 5-120 min</td>
<td>Temporal relationship established during multiple administrations. IV M discontinued and rechallenged with oral M, after which the patient went into cardiac arrest within 30 min</td>
</tr>
<tr>
<td>Authors/Year</td>
<td>Location</td>
<td>Case Details</td>
<td>Clinical Details</td>
<td>Outcome/Conclusion</td>
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<tr>
<td>Baguley et al. (1997) [30]</td>
<td>37-year-old woman</td>
<td>Given M 10 mg IV and ondansetron preoperatively; past surgical history of nausea</td>
<td>Patient experienced light-headedness, nausea, headache, vomiting, chest heaviness, and tightness in throat; ECG showed bigeminy, which later spontaneously reverted to normal sinus rhythm, as well as ST segment depression</td>
<td>Temporal relationship established. Had been previously treated with M and ondansetron without complication</td>
</tr>
<tr>
<td>Magnifico et al. (1998) [32], Magnifico et al. (2001) [33]</td>
<td>Case series in autonomic failure patients (N=11)</td>
<td>Each patient was given M 5 mg IV for 4 doses (at 5 min intervals). Doses given and measurements taken in the supine position</td>
<td>Each patient experienced a transient hypotensive effect after each dose; maximum BP drop occurred ~33 sec after each dose at 75±9 mmHg systolic and 30±3 mmHg diastolic; Transient hypotensive effect counterbalanced with reflex tachycardia</td>
<td>Hypotensive effect was noted after infusion of each dose</td>
</tr>
<tr>
<td>Chou et al. (2001) [29]</td>
<td>92-year-old female; preexisting left bundle branch block</td>
<td>IV and oral M</td>
<td>Torsade de Pointes</td>
<td>Temporal relationship. Stopped upon discontinuation</td>
</tr>
<tr>
<td>Del Campo et al. (2001) [10]</td>
<td>30-year-old male trauma patient</td>
<td>Given M 10 mg IV when enteral nutrition was started</td>
<td>Within seconds, became bradycardic and went into sinus arrest</td>
<td>Temporal relationship established. ECG taken during a subsequent dose, and heart rate decreased to 40 beats/min</td>
</tr>
<tr>
<td>Bentsen et al. (2002) [11]</td>
<td>41-year-old male, with intracerebral and subarachnoidal bleeding</td>
<td>Previously weaned off pressors two days prior to being given M 10 mg IV. M was given IV through a central venous catheter directly into the heart</td>
<td>Following administration, patient had a severe episode of asystole, with five subsequent episodes in the next 48 hours; cardiac arrests lasted 15–30 sec, one lasting two min</td>
<td>Temporal relationship established. Dopamine infusion rate was being tapered when M was started, possibly predisposing patient to bradyarrhythmias. Ascribed to rapid IV injection</td>
</tr>
<tr>
<td>Author(s)</td>
<td>Age</td>
<td>Medical History</td>
<td>Drug Dose and Administration</td>
<td>Event Description</td>
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<tr>
<td>Tung et al. (2002) [12]</td>
<td>38-year-old woman undergoing sympatholysis of left index finger due to gangrene</td>
<td>Given M 10 mg IV post-operatively. Given labetalol 10 mg IV 15 min prior; past medical history includes hypertension, pulmonary hypertension, restrictive lung disease, scleroderma</td>
<td>Within five min of M administration, developed junctional bradycardia without a pulse; eventually stabilized and required pressor support, but had another episode of bradycardia, could not be resuscitated, and expired</td>
<td>Temporal relationship established; concomitant administration of labetalol and M may have contributed to bradycarrhythmia</td>
</tr>
<tr>
<td>Grenier et al. (2003) [13]</td>
<td>66-year-old female with no history of cardiac disease. Post-mastectomy</td>
<td>Given two separate doses of M 10 mg IV postoperatively</td>
<td>One and eight min after each respective dose of M, patient experienced episodes of asystole; external cardiac massage required</td>
<td>Temporal relationship established. Same symptoms developed when rechallenged</td>
</tr>
<tr>
<td>Siddique et al. (2001) [26]</td>
<td>86-year-old male decompensated heart failure</td>
<td>M 10 mg four times daily</td>
<td>Torsade de pointes and prolonged QT syndrome requiring defibrillation</td>
<td>Normal QT interval on admission; renal impairment may have been contributory</td>
</tr>
<tr>
<td>Lau et al. (2009) [24]</td>
<td>17-year-old male with gastrinoma</td>
<td>M IV- dose and rate of administration unknown</td>
<td>BP dropped to 50/20 mmHg following M; patient inadvertently rechallenged. BP dropped to 90/50 mmHg requiring plasma expanders and inotropes</td>
<td>Temporal relationship Circulatory collapse twice when rechallenged</td>
</tr>
<tr>
<td>Schwartz et al. (2010) [14]</td>
<td>56-year-old male burn patient being treated for atrial fibrillation</td>
<td>Patient treated with digoxin. Concomitantly treated for a month with M 20 mg IV every six hours</td>
<td>After a month of concomitant digoxin and M, patient had 7 episodes of bradycardia and 15 episodes of asystole within 48 hours</td>
<td>After excluding other possibilities, digoxin and M were suspected and discontinued; hours later the bradycarrhythmias resolved</td>
</tr>
</tbody>
</table>

Abbreviations: M-metoclopramide

alter heart rate (HR). The authors attributed this effect to an α-adrenergic blocking effect but not to an antidopaminergic effect. In labetalol pre-treated hypertensive patients, HR increased about 11.5 beats per minute during CPT. BP increased from a mean of 157/97 mmHg to 193/123 mmHg (+36.8/+25.7 mmHg) [40]. The BP response was blocked by bromocriptine, a known D2-dopaminergic agonist. Moreover, the cardiovascular adverse effects do not appear to be a dose-related effect they occurred after single doses ranging from 2.5–10 mg IV [13, 15, 16].

The route of administration may be a causative factor. In all cases, metoclopramide was given IV either peripherally or via a central venous line. The rate of injection may also be causative. In a number of cases, metoclopramide was administered over seconds, not over 1–2 minutes [20]. In one study in a series of 16 patients, doses of 10 mg IV produced average decreases in systolic and diastolic BP of 22% and 20%, respectively, occurring on average 44 seconds after administration over a 10 second period [21]. The prescribing information specifically cautions that IV administration should be slow over 1–2 minutes. However, the reason stated in the package insert for slow injection is avoidance of “a transient but intense feeling of anxiety and restlessness, followed by drowsiness”, and not to avoid rapid decreases in BP or cardiovascular adverse effects [36].

**Potential Mechanisms Involved:** Metoclopramide has potent central anti-dopaminergic and peripheral cholinergic effects [1–41]. The mechanism(s) by which metoclopramide causes
cardiovascular adverse effects such as cardiac arrest is not known but may be multifactorial involving: 1) a
direct effect on the heart; 2) blockade of presynaptic
autoreceptors and enhanced catecholamine release [14,
42]; 3) other actions caused by enhancement of
cholinergic neurotransmission [5]; or 4) 5-
hydroxytryptamine (5-HT3) receptor blockade or 5-
HT4 receptor agonism [43].

Support for a mechanism involving a direct effect of
metoclopramide on the heart may be found in the
structural similarity of metoclopramide with
procainamide. Metoclopramide differs from
procainamide by only a 2,5 aryl substitution [5].
Procainamide prolongs AV conduction and may
produce tachycardia. Moreover, procainamide can also
cause peripheral vasodilation. Procainamide and
cholinergic stimulation, in general, have long been
known to cause sinus arrest [14].

The effects of metoclopramide may be due to either a
direct cardiac effect (i.e. myocardial depression) or
vasodilation. However, the BP lowering effects of
metoclopramide are unlikely to be due to a
dopaminergic mechanism but may be caused by
arteriolar vasodilation. Doses of 40 mg daily
metoclopramide reduced HR and antagonized BP
increases induced by treadmill exercise in normotensive
subjects [44].

The first potential mechanism, a direct effect is likely
to appear immediately after injection and may possibly
be linked to sodium channel blocking antiarrhythmic
effects. In four cases of cardiac arrest, the heart stopped
within 30 seconds [9–11, 16]. However, in one case
sinus arrest and bradycardia occurred 10-15 minutes
after IV administration, which suggests a different
mechanism [45].

With regard to the possible blockade of presynaptic
autoreceptors by metoclopramide, it is known that
metoclopramide enhances catecholamine release in
patients with pheochromocytoma and “essential”
hypertension [46, 47]. This results in a severe pressor
reaction with increased BP and decreased HR and is
believed to be, at least in part, mediated by vasopressin
release [41]. Metoclopramide is known to have a
striking influence on vasopressin secretion [48]. This
effect is believed to be mediated by cholinergic
stimulation. Vasopressin produces constriction of
coronary arteries (thereby reducing oxygen delivery)
and increases myocardial oxygen demand by increasing
afterload on the heart. It also increases peripheral
vascular resistance, which in turn, increases BP. In the
past, the drug was actually used to treat orthostatic
hypotension and vascular headaches because of its
vasoconstrictive effects [48]. Metoclopramide 20 mg IV
induces increased vasopressin levels in healthy patients
and type 2 diabetics [49]. In one study in hypertensive
patients, intravenously administered metoclopramide
was shown to release catecholamines [41]. One case of
cardiac arrest occurred following discontinuation of
dopamine. The long-standing influence of dopamine on
the number and function of cardiac beta 1 receptors or
the dopamine effect of release of norepinephrine in
cardiac sympathetic nerve terminals and induced
release of circulating catecholamines were postulated as
possible contributory factors. Alternatively,
metoclopramide releases acetylcholine from cholinergic
nerve terminals inducing peripheral vasodilation [43].
Studies have shown that acetylcholine levels are
increased after metoclopramide administration [51, 52].
Additionally, in vitro metoclopramide inhibited
acetylcholine to prevent its degradation [53].
Metoclopramide increases release of acetylcholine in the
CNS possibly causing cholinergic-induced
bradyarrhythmias. It is possible that the effect on the
heart may be the result of changes in cholinergic tone mimic ing vagal stimulation [29].

In animal studies, metoclopramide blocks cardiac
dopamine receptors in rats and high doses in cats
produces transient hypotensive effects [54, 55]. In other
animal studies, doses of 10 mg/kg produced bradycardia
[45, 54]. In dogs, doses of 10 mg/kg decreased systolic
and diastolic blood pressure, left ventricular systolic
pressure, and total peripheral resistance [57].

In humans, quinidine-like antiarrhythmic effects
have been observed [55, 56]. Bozzi et al. observed that
metoclopramide as a 20 mg bolus followed by 20 mg IV
at a rate of 1 mg/min had no significant effect on sinus
node conduction but did increase atrial and AV nodal
refractory periods [58].

A potential fourth mechanism for CV effects of
metoclopramide is 5-HT3 receptor blockade or 5-HT4
receptor agonism. In addition to its dopamine D2
receptor antagonist effects, metoclopramide is a mixed
5-HT3 receptor antagonist and 5-HT4 receptor agonist.
Metoclopramide’s peripheral action to increase lower
esophageal tone and gastric emptying occurs via 5HT4
receptor stimulation, whereas the antiemetic effects may
be attributed to 5HT3 receptor blockade [59, 60]. 5-HT3
receptor blockade could influence serotonin (Bezold-
Jarish reflex) causing bradycardia and hypotension [61].
Metoclopramide has also been shown to antagonize
serotonin-induced bradycardia [62]. Lau attributed
circulatory collapse from metoclopramide to excessive
serotonin autoinhibition [24].

5-HT4 receptors are also located in the heart and the
vasculature where they exert a positive chronotropic
effect and tachycardia by an action on the atrium. 5-HT4
receptor agonists are well known to exert their side
effects mainly on the lower urinary tract and the CV
system. Metoclopramide is structurally related to
cisapride, both being gastric prokinetic substituted
benzamides. Cisapride was known to trigger tachycardia
and SVT through stimulation of 5-HT4 atrial receptors.
The cardiotoxic potential of cisapride was mainly due to
QT prolongation and development of Torsades de
Pointes. This effect was deemed especially problematic
in patients concomitantly treated with drugs known to
inhibit the CYP3A4 isoenzyme [63, 64]. As recently as
cy 5 years ago, a new metabolic pathway for
metoclopramide involving the CYP2D6 isoenzyme was
identified [65]. In 100 healthy subjects, 10 mg of
metoclopramide prolonged the QT interval from 13.2±1
to 19±1 m sec [27]. Elimination of metoclopramide takes
place through hepatic metabolism involving CYP2D6. Metoclopramide elimination is likely to be slowed in poor metabolizers of CYP2D6 or those taking inhibitors of this isoform such as omeprazole [64]. It has been suggested that a toxic metabolite of metoclopramide may be linked to the tardive dyskinesia from this agent [66]. Whether or not the CV adverse effects from metoclopramide can also be linked to the CYP isoenzymes is unknown. However, since the CV adverse effects in most cases occurred immediately, a metabolic effect is deemed unlikely to have been causative.

**Future Research:** It is unlikely that further research will be undertaken as metoclopramide is available generically and there are over 10 manufacturers listed in the Orange Book. In summary, metoclopramide may occasionally cause bradycardias progressing to cardiac arrest, paroxysmal SVT, hypotension, circulatory collapse, QT prolongation, Torsade de Pointes, heart block, and hypotension in patients without evidence of underlying functional or structural cardiac abnormalities.

**CONCLUSION**

Cardiovascular CV adverse effects of metoclopramide are rare but some can be fatal. It would appear to be prudent to monitor patients receiving metoclopramide IV immediately after injection for CV adverse effects. Due to the possibility of CV risks associated with metoclopramide, it is important for clinicians to take at least some of the steps outlined in table 2. We believe it is also appropriate to warn against rapid IV injection, especially via the central venous route. Postmarketing surveillance has helped to identify rare side effects of drugs after they are on the market, but the occurrence of CV adverse effects such as bradycardia and cardiac arrest from metoclopramide which may be ascribed to an underlying disease, are probably underreported. Further, in view of the number of cases reported, we recommend additional CV adverse effects be included in the “Adverse Reactions” section of the Prescribing Information for metoclopramide. Rarely, poorly understood side effects occur with many highly effective drugs. This review should prompt a critical re-evaluation of the risk/benefit of metoclopramide and consideration of therapeutic alternatives, in concert with a search for underlying predisposing factors or mechanisms of action involved.

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